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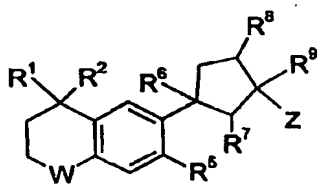

(I)

(57) Abstract

The present invention provides novel compounds of general formula (I) wherein R^1, R^2, W, Z and R^5 to R^9 are defined more fully in the description. The compounds are useful in the treatment of ailments and disorders where a reduction of the blood glucose is beneficial, such as diabetes.

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New Compounds, their Preparation and Use

FIELD OF THE INVENTION

The present invention relates to novel compounds, pharmaceutical compositions containing them, methods for preparing the compounds and their use as medicaments. More specifically, compounds of the invention can be utilised in the treatment of conditions mediated by nuclear receptors, in particular the Retinoid X Receptor (RXR) family. The compounds of the invention can also be used in combination with ligands for other nuclear receptors which are known to form dimeric complexes with RXR receptors, for example the Peroxisome Proliferator-Activated Receptor (PPAR) family.

The present compounds reduce blood glucose and triglyceride levels and are accordingly useful for the treatment of ailments and disorders such as diabetes and obesity.

BACKGROUND OF THE INVENTION

Non insulin dependant diabetes mellitus (NIDDM, type II diabetes) is a condition characterised by abnormal and ineffective insulin action and secretion. The entry of glucose from the blood into the cells of liver, skeletal muscle and adipose tissue is promoted by insulin action. In the diabetic, tissues dependant on insulin are unable to assimilate glucose normally (insulin resistance), the result being an accumulation of glucose within the blood (hyperglycemia).

Type II diabetes typically afflicts people over 40, and obesity is often a contributing factor. Regulation of diet and excercise can reduce to some extent the problems associated with NIDDM, but commonly insulin therapy or other oral hypoglycemic agents are the treatments of choice.

In addition to the range of insulin formulations, the most widely used hypoglycemic agents to date are sulphonylureas but in respective cases potentially fatal hyperinsulinemia or hypoglycemia can develop, and additional problems involving the cardiovascular, renal, neural and visual systems can also ensue.

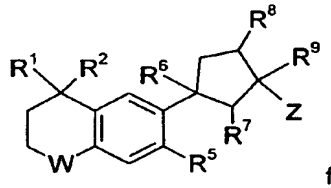
More recently, a class of compounds termed thiazolidinediones (eg. ciglitazone, pioglitazone, englitazone, troglitazone and BRL 49653), have been shown to reduce hyperglycemia by promoting insulin action without additional insulin secretion, and without causing undesirable hypoglycemia, even at elevated doses. Their effect is proposed to be a result of agonism at the PPAR receptor.

Even more recently, it has been reported that RXR agonists such as LGD 1029 and LG 100268 activate RXR/PPAR heterodimers, causing reduction in glucose, insulin and triglyc-

eride levels in ob/ob and db/db mice (Mukherjee *et al.*, *Nature* 1997, 386, 407-410, Heyman and Mukherjee WO 97/10819). This effect is due to activation at the RXR part of the heterodimer. In turn these RXR/PPAR heterodimers can also be activated by PPAR agonists (eg. thiazolidinediones) to give a similar effect, and it has been shown that at submaximal levels of either the RXR or PPAR agonist, addition of the complimentary agonist provides an additive and possibly synergistic response, and results in enhanced transcription and subsequently additional lowering of hyperglycemia, hyperinsulinaemia and hypertriglyceridaemia. It has therefore been proposed that compounds acting as agonists at the RXR receptor can be used as insulin sensitisers for the treatment of type II diabetes and related symptoms, either solely or in combination with PPAR agonists.

DESCRIPTION OF THE INVENTION

The present invention relates to retinoids of the general formula I

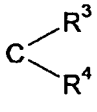


formula I

wherein

R^1 and R^2 are independently hydrogen or C_{1-6} alkyl;

W is



, O, N-R^3, S, SO or SO_2 wherein R^3 and R^4 are independently hydrogen or C_{1-6} alkyl;

R^5 is hydrogen, C_{1-6} alkyl, halogen, OR^{11}, SR^{11}, $OCOR^{11}$, NH_2, NHR^{11}, $NR^{11}R^{12}$, $NHCOR^{11}$, NR^{11}-COR^{12} where R^{11} and R^{12} are independently C_{1-6} alkyl, phenyl or alkyl phenyl;

R^6 is hydrogen, or taken together with R^7 forms a double bond, or taken together with R^7 is methylene to form a cyclopropyl ring;

R^7 is hydrogen, or taken together with R^6 forms a double bond, or taken together with R^6 is methylene to form a cyclopropyl ring, or taken together with R^9 forms a double bond, or taken together with R^9 is methylene to form a cyclopropyl ring;

R^8 is hydrogen, or taken together with R^9 forms a double bond, or taken together with R^9 is methylene to form a cyclopropyl ring

R^9 is hydrogen, hydroxy, OR^{13}, $OCOR^{13}$, or taken together with R^7 forms a double bond, or taken together with R^7 is methylene to form a cyclopropyl ring, or taken together with R^8 forms a double bond, or taken together with R^8 is methylene to form a cyclopropyl ring, where R^{13} is C_{1-6} alkyl, phenyl or alkyl phenyl;

Z is X-Y-R^{10}, wherein X is a valence bond, phenyl or pyridyl, optionally substituted with C_{1-3} alkyl, halogen, hydroxy, C_{1-3} alkoxy, C_{1-3} acyloxy, C_{1-3} alkyl halide, thiol, C_{1-3} substituted thiol, Y is C_{1-6}-alkyl, C_{2-6} alkenyl or C_{2-6} alkynyl and R^{10} is CO_2H, tetrazole, PO_3H, SO_3H, CO_2R^{15}, $CONR^{16}R^{17}$, CH_2OH, CHO, CH_2OR^{18}, $CH(OR^{19})_2$, $HC(OR^{20}O)$, COR^{21}, $CR^{20}(OR^{19})_2$, $CR^{21}(OR^{20}O)$, wherein R^{15} is C_{1-6} alkyl, phenyl or alkyl phenyl; or

Z is =Y-R^{10}, wherein Y is CR^{14}, CR^{14}-C_{1-6} alkyl, CR^{14}phenyl, CR^{14}pyridyl, $CR^{14}C_{1-3}$ alkylaryl, CR^{14}-C_{2-5} alkenyl or CR^{14}-C_{2-5} alkynyl, wherein R^{14} is H or C_{1-3} alkyl and R^{10} is CO_2H, tetrazole, PO_3H, SO_3H, CO_2R^{15}, $CONR^{16}R^{17}$, CH_2OH, CHO, CH_2OR^{18}, $CH(OR^{19})_2$, $HC(OR^{20}O)$, COR^{21}, $CR^{20}(OR^{19})_2$, $CR^{21}(OR^{20}O)$, wherein R^{15} is C_{1-6} alkyl, phenyl or alkyl phenyl;

R^{16} and R^{17} are independently hydrogen, C_{1-6} -alkyl, C_{5-8} cycloalkyl, phenyl or C_{1-6} -alkyl phenyl; R^{18} is C_{1-6} -alkyl, phenyl or C_{1-6} -alkyl phenyl; R^{19} is C_{1-6} alkyl; R^{20} is C_{2-4} alkyl; R^{21} is C_{1-6} alkyl phenyl or C_{3-6} cycloalkyl;
or a salt thereof with a pharmaceutically acceptable acid or base, or any optical isomer or mixture of optical isomers, including a racemic mixture, or any tautomeric forms

In the above structural formulas and throughout the present specification, the following terms have the indicated meaning:

The term aryl represents e.g. phenyl, pyridyl, and the like.

The terms "$C_{1-n'}$-alkyl" wherein n' can be from 2 through 15, as used herein, represent a branched or straight alkyl group having from one to the specified number of carbon atoms. Typical C_{1-8}-alkyl groups include, but are not limited to, methyl, ethyl, n-propyl, iso-propyl, butyl, iso-butyl, sec-butyl, tert-butyl, pentyl, iso-pentyl, hexyl, iso-hexyl and the like.

The terms "$C_{2-n'}$-alkenyl" wherein n' can be from 3 through 15, as used herein, represents an olefinically unsaturated branched or straight group having from 2 to the specified number of carbon atoms and at least one double bond, preferably from one to two double bonds. Examples of such groups include, but are not limited to, vinyl, 1-propenyl, 2-propenyl, allyl, iso-proppenyl, 1,3-butadienyl, 1-butenyl, hexenyl, pentenyl, and the like.

The terms "$C_{2-n'}$-alkynyl" wherein n' can be from 3 through 15, as used herein, represent an unsaturated branched or straight group having from 2 to the specified number of carbon atoms and at least one triple bond, preferably from one to two triple bonds. Examples of such groups include, but are not limited to, 1-propynyl, 2-propynyl, 1-butynyl, 2-butynyl, 1-pentynyl, 2-pentynyl and the like.

The term cycloalkyl represents e.g. cyclopropyl, cyclobutyl, cyclopentyl and the like.

The term "halogen" means fluorine, chlorine, bromine or iodine.

Certain of the above defined terms may occur more than once in the above formula I, and upon such occurence each term shall be defined independently of the other.

The compounds of the present invention may have one or more asymmetric centres and it is intended that stereoisomers (optical isomers), as separated, pure or partially purified stereoisomers or racemic mixtures thereof are included in the scope of the invention.

Preferred compounds of the present invention are:

[5-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-bicyclo[3.1.0]hex-2-ylidene]-acetic acid

[5-(5,5,8,8-Tetramethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-bicyclo[3.1.0]hex-2-ylidene]-acetic acid

4-[5-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-bicyclo[3.1.0]hex-2-ylidenemethyl]-benzoic acid

4-[5-(5,5,8,8-Tetramethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-bicyclo[3.1.0]hex-2-ylidenemethyl]-benzoic acid

6-[5-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-bicyclo[3.1.0]hex-2-ylidenemethyl]-nicotinic acid

6-[5-(5,5,8,8-Tetramethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-bicyclo[3.1.0]hex-2-ylidenemethyl]-nicotinic acid

4-{2-[5-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-bicyclo[3.1.0]hex-2-ylidene]-ethyl}-benzoic acid

4-{2-[5-(5,5,8,8-Tetramethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-bicyclo[3.1.0]hex-2-ylidene]-ethyl}-benzoic acid

6-{2-[5-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-bicyclo[3.1.0]hex-2-ylidene]-ethyl}-nicotinic acid

6-{2-[5-(5,5,8,8-Tetramethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-bicyclo[3.1.0]hex-2-ylidene]-ethyl}-nicotinic acid

4-[5-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-bicyclo[3.1.0]hex-2-en-2-yl]-benzoic acid

4-[5-(5,5,8,8-Tetramethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-bicyclo[3.1.0]hex-2-en-2-yl]-benzoic acid

6-[5-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-bicyclo[3.1.0]hex-2-en-2-yl]-nicotinic acid

6-[5-(5,5,8,8-Tetramethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-bicyclo[3.1.0]hex-2-en-2-yl]-nicotinic acid

3-[5-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-bicyclo[3.1.0]hex-2-en-2-yl]-acrylic acid

3-[5-(5,5,8,8-Tetramethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-bicyclo[3.1.0]hex-2-en-2-yl]-acrylic acid

[5-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-bicyclo[3.1.0]hex-2-en-2-yl]-propynoic acid

[5-(5,5,8,8-Tetramethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-bicyclo[3.1.0]hex-2-en-2-yl]-propynoic acid

[3-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-cyclopentylidene]-acetic acid

[3-(5,5,8,8-Tetramethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-cyclopentylidene]-acetic acid

4-[3-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-cyclopentylidenemethyl]-benzoic acid

4-[3-(5,5,8,8-Tetramethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-cyclopentylidenemethyl]-benzoic acid

6-[3-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-cyclopentylidenemethyl]-nicotinic acid

6-[3-(5,5,8,8-Tetramethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-cyclopentylidenemethyl]-nicotinic acid

4-{2-[3-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-cyclopentylidene]-ethyl}-benzoic acid

4-{2-[3-(5,5,8,8-Tetramethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-cyclopentylidene]-ethyl}-benzoic acid

6-{2-[3-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-cyclopentylidene]-ethyl}-nicotinic acid

6-{2-[3-(5,5,8,8-Tetramethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-cyclopentylidene]-ethyl}-nicotinic acid

3-Methyl-4-[5-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-bicyclo[3.1.0]hex-2-ylidene]-but-2-enoic acid

3-Methyl-4-[5-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-bicyclo[3.1.0]hex-2-ylidene]-but-2-enoic acid

3-Methyl-4-[3-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-cyclopentylidene]-but-2-enoic acid

3-Methyl-4-[3-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-cyclopentylidene]-but-2-enoic acid

3-{4-[5-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-bicyclo[3.1.0]hex-2-en-2-yl]-phenyl}-but-2-enoic acid

3-{4-[5-(5,5,8,8-Tetramethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-bicyclo[3.1.0]hex-2-en-2-yl]-phenyl}-but-2-enoic acid

3-{6-[5-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-bicyclo[3.1.0]hex-2-en-2-yl]-pyridin-3-yl}-but-2-enoic acid

3-{6-[5-(5,5,8,8-Tetramethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-bicyclo[3.1.0]hex-2-en-2-yl]-pyridin-3-yl}-but-2-enoic acid

3-{4-[4-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-cyclopent-1-enyl]-phenyl}-but-2-enoic acid

3-{4-[4-(5,5,8,8-Tetramethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-cyclopent-1-enyl]-phenyl}-but-2-enoic acid

3-{6-[4-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-cyclopent-1-enyl]-pyridin-3-yl}-but-2-enoic acid

3-{6-[4-(5,5,8,8-Tetramethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-cyclopent-1-enyl]-pyridin-3-yl}-but-2-enoic acid

4-[3-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-cyclopent-2-enyl]-benzoic acid

4-[3-(5,5,8,8-Tetramethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-cyclopent-2-enyl]-benzoic acid

6-[3-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-cyclopent-2-enyl]-nicotinic acid

6-[3-(5,5,8,8-Tetramethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-cyclopent-2-enyl]-nicotinic acid

3-{4-[3-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-cyclopent-2-enyl]-phenyl}-but-2-enoic acid

3-{4-[3-(5,5,8,8-Tetramethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-cyclopent-2-enyl]-phenyl}-but-2-enoic acid

3-{6-[3-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-cyclopent-2-enyl]-pyridin-3-yl}-but-2-enoic acid

3-{6-[3-(5,5,8,8-Tetramethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-cyclopent-2-enyl]-pyridin-3-yl}-but-2-enoic acid

4-[1-Methoxy-3-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-cyclopentyl]-benzoic acid

4-[1-Methoxy-3-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-cyclopentyl]-benzoic acid

6-[1-Methoxy-3-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-cyclopentyl]-nicotinic acid

6-[1-Methoxy-3-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-cyclopentyl]-nicotinic acid

[1-Methoxy-3-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-cyclopentyl]-propynoic acid

[1-Methoxy-3-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-cyclopentyl]-propynoic acid

3-[1-Methoxy-3-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-cyclopentyl]-but-2-enoic acid

3-[1-Methoxy-3-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-cyclopentyl]-but-2-enoic acid

4-[2-Methoxy-5-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-bicyclo[3.1.0]hex-2-yl]-benzoic acid

4-[2-Methoxy-5-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-bicyclo[3.1.0]hex-2-yl]-benzoic acid

6-[2-Methoxy-5-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-bicyclo[3.1.0]hex-2-yl]-nicotinic acid

6-[2-Methoxy-5-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-bicyclo[3.1.0]hex-2-yl]-nicotinic acid

[2-Methoxy-5-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-bicyclo[3.1.0]hex-2-yl]-propynoic acid

[2-Methoxy-5-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-bicyclo[3.1.0]hex-2-yl]-propynoic acid

3-[2-Methoxy-5-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-bicyclo[3.1.0]hex-2-yl]-but-2-enoic acid

3-[2-Methoxy-5-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-bicyclo[3.1.0]hex-2-yl]-but-2-enoic acid

4-[1-Methoxy-3-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-cyclopent-2-enyl]-benzoic acid

4-[1-Methoxy-3-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-cyclopent-2-enyl]-benzoic acid

6-[1-Methoxy-3-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-cyclopent-2-enyl]-nicotinic acid

6-[1-Methoxy-3-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-cyclopent-2-enyl]-nicotinic acid

[1-Methoxy-3-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-cyclopent-2-enyl]-propynoic acid

[1-Methoxy-3-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-cyclopent-2-enyl]-propynoic acid

alkenyl alkene

3-[1-Methoxy-3-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-cyclopent-2-enyl]-but-2-enoic acid

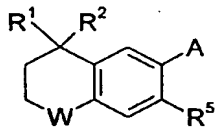
3-[1-Methoxy-3-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-cyclopent-2-enyl]-but-2-enoic acid

or a pharmaceutically acceptable salt thereof.

Pharmaceutically accepted salts of the above invention include pharmaceutically acceptable addition salts, pharmaceutically acceptable metal salts, or optionally alkylated ammonium salts, such as hydrochloric, hydrobromic, hydroiodic, phosphoric, sulphuric, trifluoroacetic, trichloroacetic, oxalic, maleic, pyruvic, malonic, succinic, citric, mandelic, benzoic, cinnamic, methanesulphonic, ethane sulphonic, picric and the like, and include acids related to the pharmaceutically acceptable salts listed (*Journal of Pharmaceutical Science* 1997, 66, 2) and incorporated herein by reference, or lithium sodium, potassium, magnesium and the like.

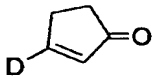
The compounds of this invention show a high degree of selectivity towards the RXR receptor family, and in particular have utility for the treatment of symptoms associated with non insulin dependant diabetes mellitus, either alone or in conjunction with PPAR selective agonists, eg. thiazolidinediones.

In accordance with the present invention compounds of formula I can be prepared by reacting a compound of formula II, wherein W, R^1, R^2 and R^5 have the meanings as defined for formula I, and where A is a suitable borate known in the art, such as a dihydroxy, dialkyl or catechol borate, or a trialkyltin or dialkyl zinc group,



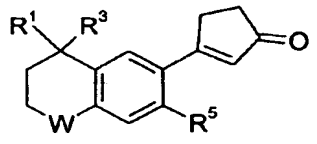
formula II

with a cyclopentenone of general formula



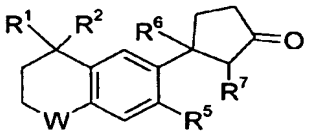
formula III

where D represents a group (for example halide, methoxy or ethoxy) which undergoes oxidative addition and cross coupling under palladium catalysis (Hegedus in *Organometallics in Synthesis*, Chapter 5, Wiley 1994) to give product of formula IV wherein W, R^1, R^3 and R^5 have the meanings as defined for formula I.



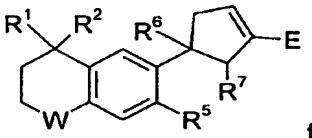
formula IV

Hydrogenation of a compound of formula IV over a palladium catalyst or cyclopropanation with for example dimethyloxosulphonium methylide (Corey *et al. J. Am. Chem. Soc.* 1963, 1353-1364) to form compounds of general formula V, wherein W, R^1, R^2 and R^5 to R^7 have the meanings as defined for formula I.



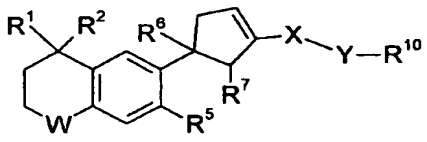
formula V

Preparation of for example the enol triflate (Ritter *Synthesis*, 1993, 735) or other group (for example vinyl halide) capable of participating in a palladium metal mediated cross coupling reaction, of a compound of general formula V using triflic anhydride and a suitable base eg. 2,6-dimethyl pyridine, to form a compound of general formula VI where E is OSO_2CF_3 (or alternatively halogen), and where W, R^1, R^2 and R^5 to R^7 have the meanings as defined for formula I.



formula VI

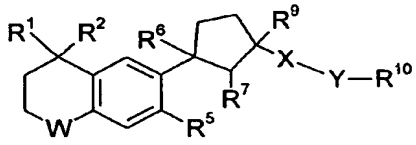
Palladium catalysed coupling of a compound of general formula VI, with a suitably metallated (for example zinc, boron, tin or magnesium) vinyl, aryl, alkynyl or alkyl group according to procedures known in the art to provide a compound of general formula VII, where W X, Y, R^1, R^2, R^5 to R^7 and R^{10} have the meanings as defined for formula I.



formula VII

Hydrogenation of a compound of general formula VII with hydrogen gas over a palladium catalyst or cyclopropanation of a compound of general formula VII with for example zinc and diiodomethane according to procedures known in the art to form a compound of general formula I, where W, X, Y, R^1, R^2, R^5 to R^7 and R^{10} have the meanings as defined for formula I.

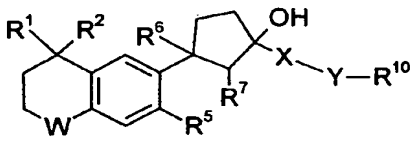
A compound of general formula V, wherein W, R^1, R^2 and R^5 to R^7 have the meanings as defined for formula I, can undergo a Wittig (for example with a ylide), Horner-Emmons (for example with a phosphonate) or Reformatsky reaction (for example with an organozinc reagent) according to procedures known in the art to give a compound of general formula VIII.



formula VIII

wherein X represents a single bond joining Y to the cycopentane ring and R^9 represents an additional bond to Y, Y is CR^{14}-C_{0-6} alkyl, CR^{14}phenyl, CR^{14}pyridyl, $CR^{14}C_{1-3}$ alkylaryl, CR^{14}-C_{2-5} alkenyl having one or two double bonds or CR^{14}-C_{2-5} alkynyl having one or two triple bonds, where R^{14} is H or C_{1-3} alkyl and wherein W, X, Y, R^1, R^2, R^5 to R^7, R^9, R^{10} and R^{14} have the meanings as defined for formula I.

Reaction of a compound of general formula V with a Grignard reagent to give a compound of general formula IX.



formula IX

where W, X, Y, R^1, R^2, R^5 to R^7, R^9 and R^{10} have the meanings as defined for formula I.

Hydroxy alkylation of a compound of formula IX with base (for example sodium hydride) and an alkyl, aryl halide or acid chloride to give a compound of formula I, where W, X, Y, R^1, R^2, and R^5 to R^{10} have the meanings as defined for formula I.

Alcohols can be prepared by reduction of carboxylic acids and derivatives (for example esters, acid chlorides) with metal hydrides. Aldehydes can be prepared by oxidation of alcohols (for example with tetrapropyammonium perruthenate or dimethylsulphoxide/oxalyl chloride) or reduction of carboxylic acid esters (for example with diisobutyl aluminium hydride). Ke-

tones can be prepared by reaction of carboxylic acid derivatives such as *N*-methyl-*N*-methoxy amides with Grignard reagents (Weinreb *Tet. Lett.* 1981, 22, 3815-3819). Ethers can be prepared from alcohols under standard Williamson conditions. Carboxylic acids can be prepared by oxidation of alcohols or aldehydes using mild oxidising agents (for example pyridinium dichromate in dimethylformamide).

In cases where a reaction may be inhibited by a reactive functional group contained in the molecule, for example alcohols, aldehydes, ketones or acids, the corresponding silyl ethers, acetals, ketals or esters can be prepared can be later removed using standard protection/deprotection protocols known in the art. (Kocienski, *Protecting Groups*, Thieme 1994). In the case of R^5 being an amino group, protection as an amide by reaction with an activated acyl group is possible, alternatively it is possible to prepare the amino group at a later stage from the corresponding aryl halide by reactions known in the art.

Molecular biology characterization of RXR activating compounds.

Competitive binding assay:

The method involves direct interaction between ligand and RXR and was analysed by displacement of RXR bound [^{3}H] 9-cis RA (retinoic acid) in a competition assay essentially as described (Levin *et al. Nature* 1992, 355, 359-361 and Heyman *et al. Cell* 1992, 68, 397-406). Briefly, extracts of infected baculovirus cells expressing recombinant RXRa is used as source of binding activity. The compound of interest is incubated in the presence of [^{3}H] 9-cis RA with RXRa containing extract. Bound probe is separated from unbound through sephadex G50 chromatography. The amount of remaining bound [^{3}H] 9-cis RA was quantitated by scintillation counting.

RXR transcriptional activation:

The activation potential of a given compound was studied in a transient trans-activation assay, essentially as described (Heyman *et al. Cell* 1992, 68, 397-406 and Tate *et al. Mol. Cel. Biol.* 1994, 14, 2323-2330). Expression plasmids encoding RXRa and a DR5 (direct repeat N_5) driven luciferase reporter plasmid was cotransfected into eucaryotic cells. Transfections also contained a plasmid constitutively expressing b-galactosidase (pCMVbgal) and carrier DNA (pGEM). 48 h after transfection cells were washed in PBS and re-fed medium containing ligand or vehicle (DMSO or Ethanol). Following overnight incubation cells were lysed and assayed for luciferse activity. Activation is expressed as the relative amount of luciferase activity (normalized to b-galactosidase activity) in treated versus untreated samples.

To determine the specificity of the ligands all were assayed on several nuclear receptors, most notably on RAR. For example, 9-cis retinoic acid (RA) activates both RXR and RAR whereas all-*trans* RA displays selectivity for RAR, (Heyman *et al. Cell* 1992, 68, 397-406).

PHARMACEUTICAL COMPOSITIONS

In another aspect, the present invention includes within its scope pharmaceutical compositions comprising, as an active ingredient, at least one of the compounds of the general formula I or a pharmaceutically acceptable salt thereof together with a pharmaceutically acceptable carrier or diluent.

Pharmaceutical compositions containing a compound of the present invention may be prepared by conventional techniques, e.g. as described in Remington: The Science and Practise of Pharmacy, 19th Ed., 1995. The compositions may appear in conventional forms, for example capsules, tablets, aerosols, solutions, suspensions or topical applications.

Typical compositions include a compound of formula I or a pharmaceutically acceptable acid addition salt thereof, associated with a pharmaceutically acceptable excipient which may be a carrier or a diluent or be diluted by a carrier, or enclosed within a carrier which can be in the form of a capsule, sachet, paper or other container. In making the compositions, conventional techniques for the preparation of pharmaceutical compositions may be used. For example, the active compound will usually be mixed with a carrier, or diluted by a carrier, or enclosed within a carrier which may be in the form of a ampoule, capsule, sachet, paper, or other container. When the carrier serves as a diluent, it may be solid, semi-solid, or liquid material which acts as a vehicle, excipient, or medium for the active compound. The active compound can be adsorbed on a granular solid container for example in a sachet. Some examples of suitable carriers are water, salt solutions, alcohols, polyethylene glycols, polyhydroxyethoxylated castor oil, peanut oil, olive oil, gelatine, lactose, terra alba, sucrose, cyclodextrin, amylose, magnesium stearate, talc, gelatin, agar, pectin, acacia, stearic acid or lower alkyl ethers of cellulose, silicic acid, fatty acids, fatty acid amines, fatty acid monoglycerides and diglycerides, pentaerythritol fatty acid esters, polyoxyethylene, hydroxymethylcellulose and polyvinylpyrrolidone. Similarly, the carrier or diluent may include any sustained release material known in the art, such as glyceryl monostearate or glyceryl distearate, alone or mixed with a wax. The formulations may also include wetting agents, emulsifying and suspending agents, preserving agents, sweetening agents or flavouring

agents. The formulations of the invention may be formulated so as to provide quick, sustained, or delayed release of the active ingredient after administration to the patient by employing procedures well known in the art.

The pharmaceutical compositions can be sterilized and mixed, if desired, with auxiliary agents, emulsifiers, salt for influencing osmotic pressure, buffers and/or colouring substances and the like, which do not deleteriously react with the active compounds.

The route of administration may be any route, which effectively transports the active compound to the appropriate or desired site of action, such as oral, nasal, pulmonary, transdermal or parenteral e.g. rectal, depot, subcutaneous, intravenous, intraurethral, intramuscular, intranasal, ophthalmic solution or an ointment, the oral route being preferred.

If a solid carrier is used for oral administration, the preparation may be tabletted, placed in a hard gelatin capsule in powder or pellet form or it can be in the form of a troche or lozenge. If a liquid carrier is used, the preparation may be in the form of a syrup, emulsion, soft gelatin capsule or sterile injectable liquid such as an aqueous or non-aqueous liquid suspension or solution.

For nasal administration, the preparation may contain a compound of formula I dissolved or suspended in a liquid carrier, in particular an aqueous carrier, for aerosol application. The carrier may contain additives such as solubilizing agents, e.g. propylene glycol, surfactants, absorption enhancers such as lecithin (phosphatidylcholine) or cyclodextrin, or preservatives such as parabenes.

For parenteral application, particularly suitable are injectable solutions or suspensions, preferably aqueous solutions with the active compound dissolved in polyhydroxylated castor oil.

Tablets, dragees, or capsules having talc and/or a carbohydrate carrier or binder or the like are particularly suitable for oral application. Preferable carriers for tablets, dragees, or capsules include lactose, corn starch, and/or potato starch. A syrup or elixir can be used in cases where a sweetened vehicle can be employed.

A typical tablet which may be prepared by conventional tabletting techniques may contain:

Core:	
Active compound (as free compound or salt thereof)	5 mg
Colloidal silicon dioxide (Aerosil)	1.5 mg
Cellulose, microcryst. (Avicel)	70 mg
Modified cellulose gum (Ac-Di-Sol)	7.5 mg
Magnesium stearate	Ad.
Coating:	
HPMC approx.	9 mg
*Mywacett 9-40 T approx.	0.9 mg

*Acylated monoglyceride used as plasticizer for film coating.

The compounds of the invention may be administered to a mammal, especially a human in need of such treatment, prevention, elimination, alleviation or amelioration of diseases related to the regulation of blood sugar.
Such mammals include also animals, both domestic animals, e.g. household pets, and non-domestic animals such as wildlife.

The compounds of the invention are effective over a wide dosage range. For example, in the treatment of adult humans, dosages from about 0.05 to about 100 mg, preferably from about 0.1 to about 100 mg, per day may be used. A most preferable dosage is about 0.1 mg to about 70 mg per day. In choosing a regimen for patients it may frequently be necessary to begin with a dosage of from about 2 to about 70 mg per day and when the condition is under control to reduce the dosage as low as from about 0.1 to about 10 mg per day. The exact dosage will depend upon the mode of administration, on the therapy desired, form in which administered, the subject to be treated and the body weight of the subject to be treated, and the preference and experience of the physician or veterinarian in charge.

Generally, the compounds of the present invention are dispensed in unit dosage form comprising from about 0.1 to about 100 mg of active ingredient together with a pharmaceutically acceptable carrier per unit dosage.

Usually, dosage forms suitable for oral, nasal, pulmonal or transdermal administration comprise from about 0.001 mg to about 100 mg, preferably from about 0.01 mg to about 50 mg of the compounds of formula I admixed with a pharmaceutically acceptable carrier or diluent.

In a further aspect, the present invention relates to a method of treating and/or preventing type I or type II diabetes.

In a still further aspect, the present invention relates to the use of one or more compounds of the general formula I or pharmaceutically acceptable salts thereof for the preparation of a medicament for the treatment and/or prevention of type I or type II diabetes.

Any novel feature or combination of features described herein is considered essential to this invention.

EXAMPLES:

The process for preparing compounds of formula I and preparations containing them is further illustrated in the following examples, which however, are not to be construed as limiting.

The structures of the compounds are confirmed by either elemental analysis (MA) nuclear magnetic resonance (NMR) or mass spectrometry (MS). NMR shifts (d) are given in parts per million (ppm) and only selected peaks are given. mp is melting point and is given in °C. Column chromatography was carried out using the technique described by W.C. Still et al, J. Org. Chem. 1978, 43, 2923-2925 on Merck silica gel 60 (Art 9385). Compounds used as starting materials are either known compounds or compounds which can readily be prepared by methods known per se.

Abbrevations:

TLC:	thin layer chromatography
DMSO:	dimethylsulfoxide
$CDCl_3$:	deutorated chloroform
DMF:	N,N-dimethylformamide
min:	minutes
h:	hours

Example 1.

3-[5-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-bicyclo[3.1.0]hex-2-ylidenemethyl]-benzoic acid

Step 1.

To a mixture of dichlorobis(triphenylphosphine)palladium(II) (220mg, 0.3mmol), sodium acetate (2.1g ,15mmol) and 3-chloro-cyclopentpent-2-enone (1.2g, 10.3mmol) in methanol (35mL) at room temperature under nitrogen was added 5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl-2-naphthaleneboronic acid (2.7g, 11mmol) and the mixture heated at reflux for 3h, cooled to room temperature and filtered through a plug of Celite. Concentration under reduced pressure gave a residue which was purified by flash chromatography to give 3-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-cyclopent-2-enone (2.0g, 73%).

^{1}H NMR ($CDCl_3$, 300MHz): 1.27 (12H, s), 1.65 (4H, s), 2.47 (3H, s), 2.53 (2H, m), 3.03 (2H, m), 6.32 (6H, m), 7.18 (1H, s), 7.42 (1H, s).

^{13}C NMR ($CDCl_3$, 75MHz):209.9, 175.7, 147.1, 142.8, 133.3, 132.5, 131.6, 129.6, 125.6, 34.9, 34.2, 34.0, 31.9, 31.8, 31.6, 21.6.

MS Calcd for $C_{20}H_{26}O$ 282.4, Found 282.8.

Step 2.

To a stirred solution 3-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-cyclopent-2-enone (6.5g, 23mmol) in methanol (175mL) at ice bath temperature was added cerium chloride heptahydrate (12.3g, 33mmol) and the whole stirred for 5min. Sodium borohydride (1.3g, 33mmol) was then added in one portion and the reaction stirred for 15min. Diethyl ether (15mL) and a mixture of brine (5mL) and dilute HCl (1mL) was added and the organic phase recovered. The aqueous phase was extracted with diethyl ether and the combined organic layers dried over sodium sulphate and concentrated to give a residue, which was purified by flash chromatography (eluant 4 hexane: 1 ethyl acetate) to give 3-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-cyclopent-2-enol (4.1g, 63%).

^{1}H NMR ($CDCl_3$, 300MHz):1.25 (12H, d), 1.55 (1H, s), 1.62 (4H, s), 1.65-1.8 (1H, m), 2.39 (3H, s), 2.32-2.48 (1H, m), 2.51-2.70 (1H, m), 2.83-2.95 (1H, m), 4.99 (1H, bs), 5.82 (m), 7.10 (1H, s), 7.13 (1H, s).

Step 3.

To a stirred solution of diethylzinc (0.59mL, 5.2mmol) dichloroethane (15mL) in an ice bath was added, dropwise, chloroiodoethane (0.76mL, 10.4mmol) forming a white suspension. After 10min 3-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-cyclopent-2-enol (1.0g, 3.5mmol) in dichloroethane (5mL) was added and the reaction stirred at this temperature for 5 min,.The reaction mixture was diluted with diethyl ether and saturated ammonium chloride (8mL) was added. The ether phase was washed with water and dried over sodium sulphate, and concentrated to give a residue, which was purified by flash chromatography (eluant 4 hexane: 1 ethyl acetate) to give 5-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-bicyclo[3.1.0]hexan-2-ol (0.51g, 49%).

^{1}H NMR ($CDCl_3$, 300MHz): 0.73 (1H, q), 1.12 (1H, t), 1.26 (12H, s), 1.64 (4H, s), 1.69-2.10 (6H, m), 2.32 (3H, s), 4.72-4.85 (1H, m), 7.02 (1H, s), 7.15 (1H, s).
^{13}C NMR ($CDCl_3$, 75MHz): 144.5, 143.6, 140.2, 136.1, 129.5, 129.1, 75.8, 36.6, 35.3, 33.6, 33.4, 33.3, 33.2, 32.9, 31.7, 31.2, 24.0, 15.6.

Step 4.

A mixture of 5-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-bicyclo[3.1.0]hexan-2-ol (610mg, 2mmol), pyridinium chlorochromate (880mg, 4mmol) and dichloromethane (40mL) was stirred for 1h at ice bath temperature. Removal of solvent under reduced pressure gave a residue, which was purified by flash chromatography (eluant 4 hexane: 1 ethyl acetate) to give 5-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-bicyclo[3.1.0]hexan-2-one (590mg, 97%).

^{1}H NMR ($CDCl_3$, 300MHz):1.71 (12H, d), 1.47 (1H, t), 1.50-1.53 (1H, m), 1.65 (4H, s), 2.03 (1H, q), 2.10-2.40 (4H, m), 2.33 (3H, s), 7.07 (1H, s), 7.11 (1H, s).
^{13}C NMR ($CDCl_3$, 75MHz): 124.8, 144.3, 142.8, 136.8, 134.6, 128.6, 127.6, 37.7, 35.2, 34.1, 33.7, 32.0, 29.7, 20.6, 19.1.

Step 5.

To a stirred suspension of sodium hydride (180mg of 60% in mineral oil, 4.5mmol) in THF (5mL) under nitrogen at ice bath temperature was added 3-(diethoxy-phosphorylmethyl)-benzoic acid methyl ester (1.3g, 4.5mmol) in THF (3mL) and the mixture stirred for 20min. A mixture of 5-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-bicyclo[3.1.0]hexan-

2-one (270mg, 0.9mmol) and 15-crown-5 (0.9mL, 4.5mmol) was added and the reaction stirred for 1h. Ice water was added and the aqueous phase extracted with diethyl ether, the combined organic layers were dried over sodium sulphate, and concentrated to give a residue, which was purified by flash chromatography (eluant 10 hexane: 1 ethyl acetate) to give a mixture of 3-[5-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-bicyclo[3.1.0]hex-2-ylidenemethyl]-benzoic acid methyl ester and 3-[5-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-bicyclo[3.1.0]hex-2-ylidenemethyl]-benzoic acid ethyl ester (390mg) which were used directly in the next step.

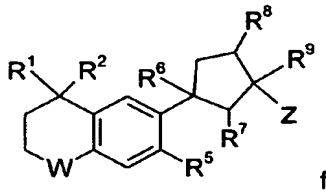
Step 6.

A mixture of 3-[5-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-bicyclo[3.1.0]hex-2-ylidenemethyl]-benzoic acid methyl ester and 3-[5-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-bicyclo[3.1.0]hex-2-ylidenemethyl]-benzoic acid ethyl ester (390mg) and aqueous potassium hydroxide (1mL of 6M) in methanol (5mL) was heated at reflux for 1h. Dilute hydrochloric acid was added and a precipitate formed. The aqueous solvent was removed and the residue triturated with water. Recrystallisation from methanol gave the title compound (40mg).

^{1}H NMR ($CDCl_3$, 300MHz):1.18 (12H, m), 1.4 (1H, m), 1.61 (4H, s), 1.90-2.10 (2H, m), 2.21 (3H, s), 2.30-2.75 (4H, m), 6.35 (1H, s), 6.99 (1H, s), 7.12 (1H, s), 7.39 (1H, t), 7.63 (1H, d), 7.89 (1H, d), 8.16 (1H, s).

CLAIMS

1. A compound of the general formula I

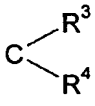


formula I

wherein

R^1 and R^2 are independently hydrogen or C_{1-6} alkyl;

W is



, O, N-R^3, S, SO or SO_2 wherein R^3 and R^4 are independently hydrogen or C_{1-6} alkyl;

R^5 is hydrogen, C_{1-6} alkyl, halogen, OR^{11}, SR^{11}, $OCOR^{11}$, NH_2, NHR^{11}, $NR^{11}R^{12}$, $NHCOR^{11}$, NR^{11}-COR^{12} where R^{11} and R^{12} are independently C_{1-6} alkyl, phenyl or alkyl phenyl;

R^6 is hydrogen, or taken together with R^7 forms a double bond, or taken together with R^7 is methylene to form a cyclopropyl ring;

R^7 is hydrogen, or taken together with R^6 forms a double bond, or taken together with R^6 is methylene to form a cyclopropyl ring, or taken together with R^9 forms a double bond, or taken together with R^9 is methylene to form a cyclopropyl ring;

R^8 is hydrogen, or taken together with R^9 forms a double bond, or taken together with R^9 is methylene to form a cyclopropyl ring

R^9 is hydrogen, hydroxy, OR^{13}, $OCOR^{13}$, or taken together with R^7 forms a double bond, or taken together with R^7 is methylene to form a cyclopropyl ring, or taken together with R^8 forms a double bond, or taken together with R^8 is methylene to form a cyclopropyl ring, where R^{13} is C_{1-6} alkyl, phenyl or alkyl phenyl;

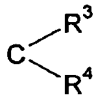
Z is X-Y-R^{10}, wherein X is a valence bond, phenyl or pyridyl, optionally substituted with C_{1-3} alkyl, halogen, hydroxy, C_{1-3} alkoxy, C_{1-3} acyloxy, C_{1-3} alkyl halide, thiol, C_{1-3} substituted thiol, Y is C_{1-6}-alkyl, C_{2-6} alkenyl or C_{2-6} alkynyl and R^{10} is CO_2H, tetrazole, PO_3H, SO_3H, CO_2R^{15}, $CONR^{16}R^{17}$, CH_2OH, CHO, CH_2OR^{18}, $CH(OR^{19})_2$, $HC(OR^{20}O)$, COR^{21}, $CR^{20}(OR^{19})_2$, $CR^{21}(OR^{20}O)$, wherein R^{15} is C_{1-6} alkyl, phenyl or alkyl phenyl; or

Z is =Y-R^{10}, wherein Y is CR^{14}, CR^{14}-C_{1-6} alkyl, CR^{14}phenyl, CR^{14}pyridyl, $CR^{14}C_{1-3}$ alkylaryl, CR^{14}-C_{2-5} alkenyl or CR^{14}-C_{2-5} alkynyl, wherein R^{14} is H or C_{1-3} alkyl and R^{10} is CO_2H, tetrazole, PO_3H, SO_3H, CO_2R^{15}, $CONR^{16}R^{17}$, CH_2OH, CHO, CH_2OR^{18}, $CH(OR^{19})_2$, $HC(OR^{20}O)$, COR^{21}, $CR^{20}(OR^{19})_2$, $CR^{21}(OR^{20}O)$, wherein R^{15} is C_{1-6} alkyl, phenyl or alkyl phenyl;

R^{16} and R^{17} are independently hydrogen, C_{1-6} -alkyl, C_{5-8} cycloalkyl, phenyl or C_{1-6} -alkyl phenyl; R^{18} is C_{1-6} -alkyl, phenyl or C_{1-6} -alkyl phenyl; R^{19} is C_{1-6} alkyl; R^{20} is C_{2-4} alkyl; R^{21} is C_{1-6} alkyl phenyl or C_{3-6} cycloalkyl;
or a salt thereof with a pharmaceutically acceptable acid or base, or any optical isomer or mixture of optical isomers, including a racemic mixture, or any tautomeric forms

2. A compound according to claim 1 wherein R^5 is hydrogen or C_{1-6}-alkyl.

3. A compound according to claim 1 or 2 wherein W is



, wherein R^3 and R^4 are independently C_{1-6} alkyl.

4. A compound according to claim 1 wherein R^6 taken together with R^7 is methylene to form a cyclopropyl ring.

5. A compound according to claim 1 wherein R^6 and R^7 are hydrogen.

6. A compound according to claim 1 wherein R^6 and R^7 form a double bond.

7. The compound according to claim 1 selected from the group consisting of [5-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-bicyclo[3.1.0]hex-2-ylidene]-acetic acid

[5-(5,5,8,8-Tetramethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-bicyclo[3.1.0]hex-2-ylidene]-acetic acid

4-[5-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-bicyclo[3.1.0]hex-2-ylidenemethyl]-benzoic acid

4-[5-(5,5,8,8-Tetramethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-bicyclo[3.1.0]hex-2-ylidenemethyl]-benzoic acid

6-[5-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-bicyclo[3.1.0]hex-2-ylidenemethyl]-nicotinic acid

6-[5-(5,5,8,8-Tetramethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-bicyclo[3.1.0]hex-2-ylidenemethyl]-nicotinic acid

4-{2-[5-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-bicyclo[3.1.0]hex-2-ylidene]-ethyl}-benzoic acid

4-{2-[5-(5,5,8,8-Tetramethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-bicyclo[3.1.0]hex-2-ylidene]-ethyl}-benzoic acid

6-{2-[5-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-bicyclo[3.1.0]hex-2-ylidene]-ethyl}-nicotinic acid

6-{2-[5-(5,5,8,8-Tetramethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-bicyclo[3.1.0]hex-2-ylidene]-ethyl}-nicotinic acid

4-[5-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-bicyclo[3.1.0]hex-2-en-2-yl]-benzoic acid

4-[5-(5,5,8,8-Tetramethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-bicyclo[3.1.0]hex-2-en-2-yl]-benzoic acid

6-[5-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-bicyclo[3.1.0]hex-2-en-2-yl]-nicotinic acid

6-[5-(5,5,8,8-Tetramethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-bicyclo[3.1.0]hex-2-en-2-yl]-nicotinic acid

3-[5-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-bicyclo[3.1.0]hex-2-en-2-yl]-acrylic acid

3-[5-(5,5,8,8-Tetramethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-bicyclo[3.1.0]hex-2-en-2-yl]-acrylic acid

[5-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-bicyclo[3.1.0]hex-2-en-2-yl]-propynoic acid

[5-(5,5,8,8-Tetramethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-bicyclo[3.1.0]hex-2-en-2-yl]-propynoic acid

[3-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-cyclopentylidene]-acetic acid

[3-(5,5,8,8-Tetramethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-cyclopentylidene]-acetic acid

4-[3-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-cyclopentylidenemethyl]-benzoic acid

4-[3-(5,5,8,8-Tetramethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-cyclopentylidenemethyl]-benzoic acid

6-[3-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-cyclopentylidenemethyl]-nicotinic acid

6-[3-(5,5,8,8-Tetramethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-cyclopentylidenemethyl]-nicotinic acid

4-{2-[3-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-cyclopentylidene]-ethyl}-benzoic acid

4-{2-[3-(5,5,8,8-Tetramethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-cyclopentylidene]-ethyl}-benzoic acid

6-{2-[3-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-cyclopentylidene]-ethyl}-nicotinic acid

6-{2-[3-(5,5,8,8-Tetramethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-cyclopentylidene]-ethyl}-nicotinic acid

3-Methyl-4-[5-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-bicyclo[3.1.0]hex-2-ylidene]-but-2-enoic acid

3-Methyl-4-[5-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-bicyclo[3.1.0]hex-2-ylidene]-but-2-enoic acid

3-Methyl-4-[3-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-cyclopentylidene]-but-2-enoic acid

3-Methyl-4-[3-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-cyclopentylidene]-but-2-enoic acid

3-{4-[5-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-bicyclo[3.1.0]hex-2-en-2-yl]-phenyl}-but-2-enoic acid

3-{4-[5-(5,5,8,8-Tetramethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-bicyclo[3.1.0]hex-2-en-2-yl]-phenyl}-but-2-enoic acid

3-{6-[5-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-bicyclo[3.1.0]hex-2-en-2-yl]-pyridin-3-yl}-but-2-enoic acid

3-{6-[5-(5,5,8,8-Tetramethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-bicyclo[3.1.0]hex-2-en-2-yl]-pyridin-3-yl}-but-2-enoic acid

3-{4-[4-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-cyclopent-1-enyl]-phenyl}-but-2-enoic acid

3-{4-[4-(5,5,8,8-Tetramethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-cyclopent-1-enyl]-phenyl}-but-2-enoic acid

3-{6-[4-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-cyclopent-1-enyl]-pyridin-3-yl}-but-2-enoic acid

3-{6-[4-(5,5,8,8-Tetramethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-cyclopent-1-enyl]-pyridin-3-yl}-but-2-enoic acid

4-[3-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-cyclopent-2-enyl]-benzoic acid

4-[3-(5,5,8,8-Tetramethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-cyclopent-2-enyl]-benzoic acid

6-[3-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-cyclopent-2-enyl]-nicotinic acid

6-[3-(5,5,8,8-Tetramethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-cyclopent-2-enyl]-nicotinic acid

3-{4-[3-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-cyclopent-2-enyl]-phenyl}-but-2-enoic acid

3-{4-[3-(5,5,8,8-Tetramethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-cyclopent-2-enyl]-phenyl}-but-2-enoic acid

3-{6-[3-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-cyclopent-2-enyl]-pyridin-3-yl}-but-2-enoic acid

3-{6-[3-(5,5,8,8-Tetramethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-cyclopent-2-enyl]-pyridin-3-yl}-but-2-enoic acid

4-[1-Methoxy-3-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-cyclopentyl]-benzoic acid

4-[1-Methoxy-3-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-cyclopentyl]-benzoic acid

6-[1-Methoxy-3-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-cyclopentyl]-nicotinic acid

6-[1-Methoxy-3-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-cyclopentyl]-nicotinic acid

[1-Methoxy-3-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-cyclopentyl]-propynoic acid

[1-Methoxy-3-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-cyclopentyl]-propynoic acid

3-[1-Methoxy-3-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-cyclopentyl]-but-2-enoic acid

3-[1-Methoxy-3-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-cyclopentyl]-but-2-enoic acid

4-[2-Methoxy-5-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-bicyclo[3.1.0]hex-2-yl]-benzoic acid

4-[2-Methoxy-5-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-bicyclo[3.1.0]hex-2-yl]-benzoic acid

6-[2-Methoxy-5-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-bicyclo[3.1.0]hex-2-yl]-nicotinic acid

6-[2-Methoxy-5-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-bicyclo[3.1.0]hex-2-yl]-nicotinic acid

[2-Methoxy-5-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-bicyclo[3.1.0]hex-2-yl]-propynoic acid

[2-Methoxy-5-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-bicyclo[3.1.0]hex-2-yl]-propynoic acid

3-[2-Methoxy-5-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-bicyclo[3.1.0]hex-2-yl]-but-2-enoic acid

3-[2-Methoxy-5-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-bicyclo[3.1.0]hex-2-yl]-but-2-enoic acid

4-[1-Methoxy-3-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-cyclopent-2-enyl]-benzoic acid

4-[1-Methoxy-3-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-cyclopent-2-enyl]-benzoic acid

6-[1-Methoxy-3-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-cyclopent-2-enyl]-nicotinic acid

6-[1-Methoxy-3-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-cyclopent-2-enyl]-nicotinic acid

[1-Methoxy-3-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-cyclopent-2-enyl]-propynoic acid

[1-Methoxy-3-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-cyclopent-2-enyl]-propynoic acid

alkenyl alkene

3-[1-Methoxy-3-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-cyclopent-2-enyl]-but-2-enoic acid

3-[1-Methoxy-3-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-cyclopent-2-enyl]-but-2-enoic acid
or a pharmaceutically acceptable salt thereof.

8. A compound according to claim 1 to 7 which acts as a RXR agonist.

9. A pharmaceutical composition comprising, as an active ingredient, a compound according to any one of claim 1 to 5 or a pharmaceutically acceptable salt thereof together with a pharmaceutically acceptable carrier or diluent.

10. A composition according to claim 9 in unit dosage form, comprising from about 0.05 to about 100 mg, preferably from about 0.1 to about 50 mg of said compound or a pharmaceutically acceptable salt thereof.

11. A compound according to claim 1 to 7 or a pharmaceutically acceptable salt thereof together with a pharmaceutically acceptable carrier or diluent for therapeutical use.

12. A pharmaceutical composition according to claim 1 to 7 for oral, nasal, transdermal, pulmonal, or parenteral administration.

13. A method for the treatment of non insulin dependant diabetes, the method comprising administering to a subject in need thereof an effective amount of a compound according to claim 1 to 7 or a pharmaceutically acceptable salt thereof, or of a composition according to any one of the preceding composition claims.

14. The method according to claim 13, wherein the effective amount of the compound according to any one of the preceding compound claims or a pharmaceutically acceptable salt or ester thereof is in the range of from about 0.05 to about 100 mg per day, preferably from about 0.1 to about 50 mg per day.

15. Use of a compound according to claim 1 to 7 or a pharmaceutically acceptable salt thereof for the preparation of a medicament.

16. Use of a compound according to claim 1 to 7 or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treatment and/or prevention of non insulin dependant diabetes

17. Any novel feature or combination of features as described herein.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/DK 99/00242

A. CLASSIFICATION OF SUBJECT MATTER

IPC6: C07C 57/50, C07C 59/72, C07C 63/44, C07C 65/24, C07D 213/60, C07D 213/24, A61K 31/19, A61K 31/44
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC6: C07C, C07D, A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CA,WPI

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Bioorgani & Medicinal Chemistry Letters, Volume 7, No 18, 1997, (Great Britain), Luc J.Farmer et al, "SYNTHESIS AND STRUCTURE-ACTIVITY RELATIONSHIPS OF POTENT RETINOID X RECEPTOR LIGANDS", page 2393 - page 2398, see particulary table 1, page 2396 --	1-16
X	Bioorganic & Medicinal Chemistry Letters, Volume 7, No 21, 1997, (Great Britain), Luc J.Farmer et al, "SYNTHESIS AND STRUCTURE-ACTIVITY RELATIONSHIPS OF POTENT CONFORMATIONALLY RESTRICTED RETINOID X RECEPTOR LIGANDS", page 2747 - page 2752, see particulary table 1,page 2750 --	1-16

[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" erlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
16 August 1999	09 -09- 1999
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Nebil Gecer Telephone No. +46 8 782 25 00

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/DK 99/00242

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 9712853 A1 (LIGAND PHARMACEUTICALS INCORPORATED), 10 April 1997 (10.04.97), see particulary compound(v) in claim 1 --	1-16
X	WO 9504036 A1 (LIGAND PHARMACEUTICALS INC.), 9 February 1995 (09.02.95), see particulary the second formula in claim 1 --	1-16
X	WO 9415902 A1 (LIGAND PHARMACEUTICALS INC), 21 July 1994 (21.07.94) --	1-16
X	WO 9321146 A1 (LIGAND PHARMACEUTICALS INCORPORATED), 28 October 1993 (28.10.93) -- ---	1-16

INTERNATIONAL SEARCH REPORT

International application No.
DK99/00242

Box I **Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)**

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 13-14
because they relate to subject matter not required to be searched by this Authority, namely:

Claim 13-14 are directed to methods of treatment of the human or animal body by therapy methods practised on the human or animal body (see PCT, Rule 39.1)). Nevertheless, a search has been

.../...

2. ☒ Claims Nos.: 17
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

Claim 17 does not comply with Art.6. PCT prescribing that claims shall be clear and concise.

Box II **Observations where unity of invention is lacking (Continuation of item 2 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

executed for these claims. The search has been based on the alleged effects of the compounds/compositions.

INTERNATIONAL SEARCH REPORT

Information on patent family members

02/08/99

International application No.
PCT/DK 99/00242

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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		AU 7362496 A	28/04/97
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		NO 981501 A	02/06/98
		WO 9710819 A	27/03/97
WO 9504036 A1	09/02/95	AT 177733 T	15/04/99
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		SE 0678087 T3	
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		JP 8505359 T	11/06/96
		JP 8505852 T	25/06/96
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		MX 9306627 A	29/07/94
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		NO 303936 B	28/09/98
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		US 5780676 A	14/07/98
		WO 9321146 A	28/10/93
		WO 9415901 A	21/07/94
		WO 9415902 A	21/07/94

INTERNATIONAL SEARCH REPORT

Information on patent family members

02/08/99

International application No.
PCT/DK 99/00242

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9415902 A1	21/07/94	AU 691477 B	21/05/98
		AU 5586894 A	15/08/94
		BR 9307784 A	14/11/95
		EP 0678086 A	25/10/95
		JP 8505852 T	25/06/96
		AT 177733 T	15/04/99
		AU 675430 B	06/02/97
		AU 4118893 A	18/11/93
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